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Mutations in the retinoblastoma-related gene RB2/p130 in lung tumors and suppression of tumor growth in vivo by retrovirus-mediated gene transfer.

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The retinoblastoma (Rb) family consists of the tumor suppressor pRb/p105 and related proteins p107 and pRb2/p130. Recent immunohistochemical studies of the retinoblastoma family of proteins in 235 specimens of lung cancer show the tightest inverse association between the histological grading in the most aggressive tumor types and pRb2/p130. This led us to study a panel of human lung cancers for mutations in the RB2/p130 gene. Mutations in the Rb-related gene RB2/p130 were detected in 11 of 14 (78.5%) primary lung tumors by single-strand conformation polymorphism and sequence analysis. A Moloney leukemia virus-based retroviral system was set up, and a comparable viral concentration of 1 x 10(7) infectious units/ml was obtained. Retrovirus-mediated delivery of wild-type RB2/p130 to the lung tumor cell line H23 potently inhibited tumorigenesis in vitro and in vivo, as shown by the dramatic growth arrest observed in a colony assay and the suppression of anchorage-independent growth potential and tumor formation in nude mice. The tumors transduced with the RB2/p130 retrovirus diminished in size after a single injection, and a 12-fold reduction in tumor growth after RB2/p130 transduction compared with the Pac-transduced tumors (92% reduction, $P = 0.003$) and lacZ-transduced tumors (93% reduction, $P < 0.001$) was found to be statistically significant. These findings provide the missing confirmation that RB2/p130 is a "bona fide" tumor suppressor gene and strengthen the hypothesis that it may be a candidate for cancer gene therapy for lung cancer.

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